CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-061 and 21-062

APPROVAL LETTER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-061
NDA 21-062

DEC 17 1999

Bristol-Myers Squibb Pharmaceutical Research Institute
Attention: Douglas C. Kriesel, Ph.D.
Director, Worldwide Regulatory Affairs
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Dear Dr. Kriesel:

Please refer to your new drug application (NDA) dated December 28, 1998, received December 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tequin™ (gatifloxacin) Tablets, 200mg and 400mg, and Tequin™ (gatifloxacin) Injection, 10mg/mL (200mg) 20mL vials, 10mg/mL (400mg) 40mL vials, 2mg/mL (200mg) 100-mL flexible container, and 2mg/mL (400mg) 200-mL flexible container.

We aeknowledge receipt of your submissions dated:

December 28, 1998
January 27, 1999
January 29, 1999
February 5, 1999
February 10, 1999 (2)
February 12, 1999
March 19, 1999
March 23, 1999
April 7, 1999
April 9, 1999
April 16 1999
May 5, 1999
May 10, 1999
May 27, 1999
June 11, 1999
July 12, 1999
July 13, 1999
July 20 ,1999
July 21 1999
August 6, 1999
August 12, 1999
August 13, 1999
August 20, 1999
August 25, 1999
August 27, 1999
September 2, 1999
September 3 ,1999
September 16, 1999
September 21 ,1999
September 21, 1999
September 24, 1999
October 8, 1999 (3)
October 22, 1999
October 29, 1999
November 2, 1999
November 4, 1999
November 22, 1999
December 3, 1999 (2)
December 8, 1999 (2)
December 10, 1999
December 14, 1999
December 15, 1999
December 16, 1999 (2)
December 17, 1999 (2)

These new drug applications provide for the use of Tequin™ (gatifloxacin) for Community-Acquired Pneumonia; Acute Bacterial Exacerbation of Chronic Bronchitis; Acute Sinusitis; Uncomplicated Skin and Skin Structure Infections; Uncomplicated Urinary Tract Infections; Complicated Urinary Tract Infections and Pyelonephritis; Uncomplicated Urethal, Pharyngeal,

and Rectal Gonorrhea in Males; as well as Endocervical, Pharyngeal, and Rectal Gonorrhea in Females.

We have completed the review of these applications, as amended. We have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling submitted December 17, 1999, for community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute bacterial sinusitis, uncomplicated urinary tract infections, complicated urinary tract infections, pyelonephritis, and uncomplicated gonorrhea. Accordingly, the applications are approved effective on the date of this letter.

In addition, we have concluded that the indication of [redacted] is approvable pending submission of post-marketing data confirming the safety of gatifloxacin and therefore demonstrating an acceptable risk/benefit profile. These data will be obtained from completion of Phase 4 commitments 1 through 6 listed below.

The Phase 4 commitments to which Bristol-Myers Squibb Company agreed in its submission dated December 16, 1999, along with any completion dates agreed upon, are listed below:

1. To better understand the risk/benefit profile of oral gatifloxacin, Bristol-Myers Squibb will review post-marketing adverse event data following at least one million patient exposures worldwide. A substantial proportion of these exposures will be from the United States. The results of this evaluation will be submitted to the Division by December 31, 2000.

2. Bristol-Myers Squibb will conduct and submit the results of an active surveillance program. The results of this program will provide information on the incidence of adverse events for at least 15,000 patients using gatifloxacin tablets and/or gatifloxacin injection. Please submit protocols and methods for this study to the Division within ninety days of receipt of this letter. A report on this experience will be submitted to the Division by December 31, 2000.

3. Bristol-Myers Squibb will conduct a study of the effect of gatifloxacin on the QTc interval by studying its effect in patients receiving gatifloxacin in currently ongoing studies. Pre-dose and post-dose valid electrocardiograms and concurrent gatifloxacin serum concentrations should be performed. The results of this study should be submitted to the Division by December 31, 2000.

4. Bristol-Myers Squibb will conduct a gatifloxacin single oral dose escalation study of the effects on QTc at Cmax. The results of this study will be submitted to the Division by December 31, 2000.

5. Bristol-Myers Squibb will conduct a study to compare the effects of gatifloxacin, ciprofloxacin, clarithromycin and sparfloxacin on QTc at Cmax. The results of this study will be submitted to the Division by December 31, 2000.

6. The pharmacokinetic studies described in items 3, 4 and 5 will include equal number of men and women over a broad range of ages (≥18 years; including geriatric patients).

7. Bristol-Myers Squibb will repeat the rat oral and intravenous teratology studies using adequately high dose levels. The results of these studies will be submitted to the Division by December 31, 2000.

The Division anticipates discussing the details of the above studies at your earliest convenience.

Protocols, data, and final reports for the Phase 4 commitments should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition to the above Phase 4 commitments, we suggest that Bristol Myers Squibb consider conducting the following studies:

1. Bristol-Myers Squibb should consider extending the understanding of the effect of gatifloxacin on the rapidly-activating delayed-rectifier current compared to additional members of the quinolone class by adding them to your *in vitro* HERG model (e.g., levofloxacin). Bristol Myers Squibb may also wish to consider testing gatifloxacin in the AT-1 model.

2. Bristol-Myers Squibb should consider performing another study in the anesthetized beagle model with higher intravenous doses of gatifloxacin and concurrent measurements of gatifloxacin plasma concentration with cardiac monitoring so that the rhythm/concentration relationship could be studied at the higher, potentially toxic levels.

3. Bristol-Myers Squibb should consider conducting a gatifloxacin single dose drug interaction study with aluminum/magnesium antacids to determine the appropriate time for dosing gatifloxacin AFTER antacids are taken.

4. Bristol-Myers Squibb should consider approaches to evaluating potential pharmacodynamic interactions effecting QTc length between gatifloxacin and class IA and III antiarrhythmics.

The final printed labeling (FPL) must be identical to the submitted labeling dated December 17, 1999 (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-061 and NDA 21-062". Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact D. Laurie Bernato, R.N., MN, Regulatory Project Manager, at (301) 827-2127.

Sincerely yours,

/S/

Sandra L. Kweder, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure